Appendices

1. Questionnaire

Question 1
How is off-label prescription of medicinal products regulated by law?

Could you attach the relevant articles of law in English and the corresponding website where possible?

Question 2
How is off-label prescription of medicinal products regulated by jurisprudence and literature?

Could you attach the relevant case law and scientific articles in English and the corresponding websites where possible?

Question 3
What is the prevalence of off-label prescription of medicines in general and with respect to pediatric and geriatric populations?

Could you attach the relevant scientific articles in English and the corresponding websites where possible?

Question 4
What motives mainly drive of off-label prescription? Choose from either healthcare motives or economic motives and describe where possible the corresponding subcategories of the motives.

Could you attach the relevant and scientific articles in English and the corresponding websites where possible?

2. List of prerequisites for classification of legislation regarding off-label prescription

Prerequisite	Frequency	MS(s)
Absence of an alternative (on-label) treatment	1	Bulgaria
Scientific evidence and proven experience/clinical practice	4	Bulgaria, Finland, Czech Republic, Sweden
Assessment by special committee of physicians	1	Bulgaria
Prescription in hospital care	1	Bulgaria
Informed patient consent	5	Bulgaria, Germany, Estonia, the Netherlands, Sweden
Informing the patient of the consequences of the treatment	4	Czech Republic, Germany, Estonia, the Netherlands
Notification of a policy organ	3	Bulgaria, Czech Republic, Sweden
Monitoring and documenting the treatment	1	Bulgaria
No payment of the off-label treatment with public funds	1	Bulgaria
Conventional methods are not likely to be as effective	1	Estonia
Positive risk/benefit balance compared to on-label/conventional treatment	1	Estonia
Marking the prescription in case of deviation from the authorised dose	1	Finland
Developed standards or protocols	1	The Netherlands
Consultation between physician and pharmacist	1	The Netherlands

Table B1. Prerequisites for off-label prescription of all MS.

3. Declaration on Good Off-Label Use in Practice

The five GOLUP principles are:

1. “Presence of a medical therapeutic need based on a current examination of the patient by a suitably qualified health care professional;
2. Absence of authorised treatment and licensed alternatives tolerated by the patient or repeated treatment failure;
3. A documented review and critical appraisal of available scientific evidence favours off-label use to respond to the unmet medical need of the individual patient
4. Patients (or their legal representative) must be given sufficient information about the medicines that are prescribed to allow them to make an informed decision;
5. Presence of established reporting routes for outcomes and adverse events linked to off-label use.”[12].

The general aim of GOLUP reads:

“While not optimal, off-label prescribing may remain essential to address unmet medical needs of patients. However, the manner in which countries deal with the off-label use of medicines is not harmonised across the EU. 2 In this context, some EU Member States have passed legislation that promotes the off-label use of medicines for economic purposes. These developments endanger agreed European scientific standards, thus putting patients’ safety at risk. We thus highlight the importance of preserving the European regulatory framework to ensure the safety of patients, while ensuring good off-label use of medicines for patients in need. Therefore, it is necessary to summarize the principles of Good Off-Label Use Practice (GOLUP) to guide practice as it currently exists in different Member States of the EU.

The following GOLUP principles stem from decades of research and clinical practice and serve to create a framework to ensure that the interests of patients, prescribers, pharmacists and the public at large are protected. The signatories of this declaration call on the European Medicines Agency and other national regulatory bodies to adopt strict guidelines to support healthcare practitioners in ensuring safe drug therapy when licensed medicines do not meet the needs of the individual patient, while making sure that public health remains a priority and is not undermined by economic interests.” [12].

4. Full list of categorical elements in law

Categorical element	Count	MS
Distinction between non-authorised medicinal products and off-label use/prescription	5	Bulgaria, Czech Republic, Germany, the Netherlands, Slovenia
No distinction between non-authorised medicinal products and off-label use/prescription	5	Estonia, Finland, Ireland, Romania, Sweden
Professional freedom of physician	4	Bulgaria, Germany, Romania
Professional standards of physician	2	the Netherlands, Romania
Medical standards/medical ethics	1	Bulgaria, Romania
Definition or reference to off-label use/prescription	5	Bulgaria, Czech Republic, Germany, the Netherlands, Slovenia
No definition or reference to off-label use/prescription	5	Estonia, Finland, Ireland, Romania, Sweden
Prerequisite of absence of an alternative (on-label) treatment	1	Bulgaria
Prerequisite of scientific evidence and proven experience/clinical practice	4	Bulgaria, Finland, Czech Republic, Sweden
Prerequisite of assessment by special committee of physicians	1	Bulgaria
Prerequisite of prescription in hospital care	1	Bulgaria
Prerequisite of informed patient consent	5	Bulgaria, Germany, Estonia, the Netherlands, Sweden
Prerequisite of informing the patient of the consequences of the treatment	4	Czech Republic, Germany, Estonia, the Netherlands
Prerequisite of notification of a policy organ	3	Bulgaria, Czech Republic, Sweden
Prerequisite of monitoring and documenting the treatment	1	Bulgaria
Prerequisite of not paying the off-label treatment with public funds	1	Bulgaria
Prerequisite that conventional methods are not likely to be as effective	1	Estonia
Prerequisite of positive risk/benefit balance compared to on-label/conventional treatment	1	Estonia
Prerequisite of marking the prescription in case of deviation from the authorised dose	1	Finland
Prerequisite of developed standards or protocols	1	The Netherlands
Prerequisite of consultation between physician and pharmacist	1	The Netherlands
Conditions regarding reimbursement for off-label products	1	Germany
Prohibition of promotion of off-label products	1	Ireland
Requirement of reporting adverse reactions of off-label prescribed/used products	1	Slovenia
Consequences/conditions responsibility in case of off-label prescription	2	Czech Republic, Ireland

5. Explicit regulations regarding off-label prescription

MS	Regulation/Law source	Corresponding law text
Bulgaria	Law on Medicinal products in Human Medicine Article 266b(1)	Exceptionally, in the absence of an alternative for the treatment of a specific patient and only in the interest of his health, a medicinal product authorized for use in the country may be administered outside the conditions of the marketing authorization for the medicinal product, provided that there is scientific evidence of the safety and efficacy of that product.[1]
Czech Republic	Act. No. 378/2007 Coll. on Pharmaceuticals and on Amendments to Some Related Acts Section 8(4)	If a medicinal product is not distributed or if a medicinal product of the required therapeutic properties is not marketed, the attending medical doctor may use an authorised medicinal product in a manner which is not consistent with the summary of the product characteristics, if sufficient scientific grounds exist for the application of such method.[2]
Germany	German Social Code Book 5 Section 35c(1)	The Federal Ministry of Health appoints expert groups at the Federal Institute for Drugs and Medical Devices, at least one of them, to provide assessments of the state of scientific knowledge about the use of approved drugs for indications and areas of indication for which they are not approved under the Drugs Act Permanent expert group, which can be supplemented depending on the subject. […] The Federal Joint Committee can commission the expert groups to carry out assessments in accordance with sentence 1; he regulates the details in his rules of procedure. The Federal Ministry of Health can also commission assessments according to sentence 1. The assessments are forwarded to the Federal Joint Committee as a recommendation for a resolution in accordance with Section 92 (1) sentence 2 number 6. Reviews should only be made with the consent of the pharmaceutical company concerned. Separate actions against these evaluations are inadmissible.[3]
The Netherlands	Medicines Act 2007 Article 68(1)	Prescribing outside the indications registered by the Medicines Evaluation Board is only permitted when protocols or standards have been developed by the professional group. If the protocols and standards are still under development, consultation between the treating physician and pharmacist is necessary.[4]
Slovenia	Medicinal Products Act	Defines off-label use as any intentional use of a product for medical purposes that is not consistent with its marketing authorisation.[5]

[1] Translation from Bulgarian law text made by an EMACOLEX member who represents Bulgaria.
[2] Translation from Czech law text made by an EMACOLEX Member who represents the Czech Republic.
[3] Translation from German law text from https://www.gesetze-im-internet.de/englisch_bgb/index.html.
[4] Translation from Dutch law text made by an EMACOLEX Member who represents the Netherlands.
[5] Response of EMACOLEX Member from Slovenia. We must ask for the original law text.

6. Number of regulations and national legislation references of the regulations per Member State

MS	Regulation nr. 1	Regulation nr. 2	Regulation nr. 3	Regulation nr. 4	Regulation nr. 5
Bulgaria	Law on Medicinal products in Human Medicine Article 266b				
Czech Republic	Act. No. 378/2007 Coll. on Pharmaceuticals and on Amendments to Some Related Acts Section 8				
Estonia	Law of Obligations Act § 763				
Finland	Decree of the Ministry of Social Affairs and Health (1088/2010) Section 10	Decree of the Ministry of Social Affairs and Health (1088/2010) Section 13			
Germany	German Social Code Book 5 Section 35c	Federal Medicinal Regulations Section 1(1)	German Civil Code Section 630c	German Civil Code Section 630d	German Civil Code Section 630e
Ireland	Statutory Instrument 540/2007, Medicinal Products (Control of Placing of the Market) Regulations 2007, Regulation 6(4)	Statutory Instrument 540/2007, Medicinal Products (Control of Placing of the Market) Regulations 2007, Schedule 1, paragraphs 2 and 3			
The Netherlands	Medicines Act 2007 Article 68 Gnw	Dutch Civil Code Article 7:448	Dutch Civil Code Article 7:450(1)	Dutch Civil Code Article 7:453	
Romania	Law no. 95/2006 on Healthcare Reform Article 241	Law no. 95/2006 on Healthcare Reform Article 381			
Slovenia	Medicinal Products Act	Medicinal Products Act Article 129			
Sweden	Patient Safety Act (2010: 659) Chapter 6 Section 1	Patient Act (2014:821) Chapter 4 Section 2			